

Institute of Clinical Epidemiology, National Institutes of Health, UP Manila In cooperation with the Philippine Society for Microbiology and Infectious Diseases Funded by the Department of Health

EVIDENCE SUMMARY

RESEARCH QUESTION: Among COVID-19 patients, should remdesivir be used for treatment?

Latest Update by: Carol Stephanie C. Tan Lim, MD, MSc, Natasha Ann R. Esteban-Ipac, MD, Mario M. Panaligan, MD, Ivan N. Villespin, MD, Arnel Gerald Q. Jiao, MD, Marissa M. Alejandria, MD, MSc Previous Update by: Adult COVID-19 CPG - Carol Stephanie C. Tan Lim, MD, MSc, April P. Padua-Zamora, MD Mary Christine Castro, MD, MSc Pediatric COVID-19 CPG - Melissa A. Dator, MD, Ma. Lucila M. Perez, MD, MSc, Maria Teresa S.

RECOMMENDATIONS

Tolosa, MD, DipCE, Leonila F. Dans, MD, MS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of remdesivir among hospitalized adult patients with mild to moderate COVID-19 infection with at least 1 risk factor* for progression to severe disease.	Low	Weak
*60 years old or older, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30), immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, or sickle cell disease		
We recommend the use of remdesivir among non-hospitalized adult patients with mild to moderate COVID-19 infection with at least 1 risk factor* for progression to severe disease.	Moderate	Strong
*60 years old or older, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30), immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, or sickle cell disease		
We suggest the use of remdesivir in children (hospitalized or ambulatory) with mild to moderate COVID-19 infection with at least 1 risk factor for disease progression.	Very low	Weak
We suggest the addition of remdesivir to dexamethasone in adult patients with COVID-19 infection requiring oxygen supplementation but do not require mechanical ventilation*. *For patients who progress to invasive mechanical ventilation while	Low	Weak
on remdesivir, the drug can be continued.		
We suggest the addition of remdesivir to dexamethasone in children with COVID-19 infection requiring oxygen supplementation but do not require mechanical ventilation.	Very low	Weak
We suggest against the use of remdesivir among adult patients with COVID-19 infection who are already on non-invasive or invasive mechanical ventilation.	Low	Weak



We suggest against the use of remdesivir among children with COVID-19 infection who are already on non-invasive or invasive mechanical ventilation.	Very low	Weak

Consensus Issues

The panel issued separate recommendations for hospitalized and non-hospitalized adult patients with mild to moderate COVID-19, mainly due to different treatment duration (3 days for non-hospitalized vs 5 days for hospitalized) and critical outcomes measured (need for hospitalization or ER visit for non-hospitalized; need for mechanical ventilation and clinical deterioration for hospitalized). Like other antivirals, benefit of remdesivir is expected to be greater if given early in the disease course. Outpatients are more likely to receive remdesivir early in their disease course, hence are more likely to benefit from the drug's antiviral activity. This is in contrast to hospitalized patients who are more likely to receive remdesivir during the latter phase of their disease course. However, the panel also considered the high resource requirements in giving remdesivir to outpatients with mild to moderate COVID-19. The three-day regimen will require intravenous home infusions or multiple visits to the emergency room for the infusion.

With the introduction of vaccines against COVID-19, patients are more likely to have mild to moderate COVID-19, not requiring admission unless with risk factors for disease progression. The panel recognized that there are instances wherein adult patients are admitted due to other condition(s) and incidentally have mild-moderate COVID-19 infection as well. The panel believed that since there is evidence supporting use of remdesivir in hospitalized patients with mild to moderate COVID-19, this treatment option ought to be made available to this subgroup of patients, albeit low certainty of evidence. Only 1 of the 10 RCTs excluded vaccinated patients (outpatient study) while the rest did not mention the participants' vaccination status, since most RCTs on hospitalized COVID-19 patients were done early in the COVID-19 pandemic and prior to vaccine rollout. Hence, the panel did not include vaccination status as one of the qualifiers in the current recommendations.

The panel did not specify age in the recommendations for children, because randomized controlled trials (RCTs) specific to the pediatric population are still lacking. There was only 1 RCT on outpatients which explicitly reported inclusion of 8 adolescents (12-18 years old). Hence, the recommendations for children were extrapolated from adult studies and certainty of evidence was further downgraded due to indirectness. Recommendations from other groups vary, depending on the country's regulatory approval. US NIH recommends remdesivir for children 12 to 17 years of age, while Australian COVID-10 guidelines states that remdesivir may be given to children at least 28 days old and weighing at least 3kg.

KEY FINDINGS

- A total of 10 RCTs on the use of remdesivir in treatment of COVID-19 were included in this review.
- Remdesivir showed significant benefit for outpatients with mild to moderate disease with at least one risk factor for disease progression in terms of COVID 19-related and all-cause hospitalizations, and need for medically-attended visits.
- For hospitalized patients, remdesivir had a slight benefit in reducing all-cause mortality at day 28.
- Subgroup analysis by disease severity showed a trend towards reduction in mortality among those with severe disease, with no effect on those with critical disease and inconclusive effect for those with mild-moderate disease.
- Subgroup analysis by oxygen requirement showed trend towards mortality reduction for patients on low and high flow oxygen, and a trend towards increased mortality for those on mechanical ventilation.
- There was inconclusive effect on those without oxygen support.
- Remdesivir showed benefit in decreasing clinical deterioration, improving recovery rate, and reducing the need for mechanical ventilation.
- There was inconclusive effect on the need for ICU admission.
- No increased risk of adverse events, including serious adverse events, was seen.



• The overall certainty of evidence was low due to serious risk of bias AND inconsistency or imprecision in several critical outcomes.

WHAT'S NEW IN THIS VERSION?

This update contains the final results of the WHO solidarity trial and the DisCoVeRy trial.

PREVIOUS RECOMMENDATIONS

As of 19 February 2021

We suggest against the use of remdesivir in patients with COVID-19 infection who have O_2 saturation \geq 94% and do not require oxygen supplementation. (Low certainty of evidence; conditional recommendation)

We suggest the addition of remdesivir to dexamethasone in patients with COVID-19 infection who have O2 saturation <94% and/or requiring oxygen supplementation*. (Low certainty of evidence; conditional recommendation)

*For patients who progress to invasive mechanical ventilation while on remdesivir, the drug can be continued.

We suggest against the use of remdesivir in patients with COVID-19 infection who are already on invasive mechanical ventilation. (Low certainty of evidence; Conditional recommendation).

We suggest the use of remdesivir in hospitalized children with severe COVID-19 infection. (Very low certainty of evidence; Weak recommendation)

We suggest the use of remdesivir in non-hospitalized children with COVID-19 infection with at least 1 risk factor for disease progression. (Low certainty of evidence; weak recommendation)

Previous Consensus Issues

Consensus Panel for Adult COVID-19

Early introduction of remdesivir in the treatment of COVID-19 is preferred because of its action on the polymerase resulting to less viral replication. Remdesivir is a relatively safe drug, however, its cost should be considered. Hence, routine use of the drug is not recommended. There are 26 ongoing trials pertaining to the efficacy and safety of remdesivir for the treatment of COVID-19.

Consensus Panel for Pediatric COVID-19

The recommendations were based on the evidence from one observational study among pediatric patients and 10 randomized controlled trials among patients aged 12 years old and above.

Despite the very low certainty of evidence for hospitalized children, the panel voted for the use of remdesivir. This is due to the significant benefit in decreasing the risk for clinical deterioration (based on WHO progression scale) and the risk reduction in mechanical ventilation use, although this was not statistically significant. The panel also agreed that because there are very limited treatment options for pediatric patients with COVID-19, this would give better guidance to clinicians. The panel emphasized though that remdesivir should be used for pediatric patients with severe COVID-19 following the classification of PIDSP and PSMID (on low flow oxygen support).

The panel voted for the use of remdesivir in non-hospitalized children with COVID-19 infection based on the evidence from one double-blind, placebo-controlled randomized controlled trial done among patients aged 12 years old and above. This study showed significant benefit in preventing COVID-19 related hospitalization or all-cause mortality. Remdesivir was given to the patients 7 days from symptom onset and to those with at least one of the following risk factors: hypertension, cardiovascular or



cerebrovascular disease, diabetes mellitus, obesity, immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer or sick cell disease.

INTRODUCTION

Remdesivir is an intravenously administered antiviral drug originally developed for the Ebola virus that is currently being evaluated as a potential treatment for COVID-19. It is a nucleotide analogue that inhibits RNA-dependent RNA polymerase [1]. In vitro studies and studies in animal models have demonstrated its antiviral activities against an array of RNA viruses (e.g., MERS-CoV, Ebola, and SARS-CoV) [2-4]. An in vitro study has shown that remdesivir can inhibit the growth of the COVID-19 virus in infected Vero cells and can inhibit infection in human cell lines [5].

REVIEW METHODS

A systematic search was done from the date of last search January 26, 2022 until September 4, 2022 in Medline, Cochrane Library, and MedRivx. We used a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and remdesivir. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Randomized controlled trials on remdesivir compared to placebo or standard of care in the treatment of COVID-19, regardless of severity and age, were included. A few meta-analysis from the COVID-NMA was adopted in this review. Subgroup analysis by disease severity and level of oxygen requirement was planned. For studies that reported aggregate data on overlapping subgroup categories, the data was placed in the more severe subgroup/higher level of oxygen requirement subgroup.

RESULTS

Characteristics of the included studies

This update includes a total of ten (10) studies covering 13,285 participants [6-16]. Nine of the included studies recruited confirmed COVID-19 patients needing hospitalization, while one study [14] limited recruitment to non-hospitalized patients. The severity of disease of the study participants were mild to critical in four studies, mild to moderate in two studies, mild to severe in one study, moderate to severe in one study, severe in one study, and unclear in one study. All studies involved adult patients. The study on non-hospitalized patients included study participants 12 years old and above, but only 8 participants belonged to the 12 to 18 year old age group. There were no RCTs on children. The median duration of symptoms before randomization and treatment initiation range from 8 to 10 days in five studies [6,8,9,11,15]; while one study reported a 7-day mean duration of symptoms before hospital admission [12]. Only two studies reported recruiting patients within 7 days of symptom onset [13,14]. Studies were mostly conducted in high and upper-middle income countries. Eight RCTs used a 10-day course of remdesivir [6-9,11,12,13,15], two studies used a 5-day course [10,11], and the study in outpatients used a 3-day course [14]. Remdesivir was compared to placebo in 1 study [14], while the rest compared remdesivir to the local standard of care [6-13,15]. Standard of care allowed the use of corticosteroids in seven of the studies [6-7,9-12,15]. Other potential COVID-19 treatments were being investigated in parallel to remdesivir in two multi-arm trials [7,12].

The primary outcome in all studies was all-cause mortality, with duration of follow-up ranging from 24 to 90 days [6-15]. Clinical status or improvement was reported by all studies, using variable 6-, 8-, or 10-point scales. The outcomes of five studies with sufficient description of this outcome measure were converted to the WHO ordinal scale for pooled analysis [6,8-11]. Other outcomes reported were time to clinical improvement or recovery [5,8,9,11], need for mechanical ventilation [7-9,11,12,13,15], duration of hospital stay [7,13,15], need for ICU admission [12], adverse event s[6,8,9,11,13,14,15], and serious adverse events [6,8,9,11,14,15,16]. Characteristics of included studies are summarized in Appendix 2.



Certainty of evidence

The overall certainty of evidence was low due to serious risk of bias AND inconsistency or imprecision in several critical outcomes. The serious risk of bias was due to concerns in selection, performance bias, detection bias, attrition bias, and reporting bias in most of the included studies. The risk of bias summary is in Appendix 3. The GRADE evidence summary is in Appendix 4.

Effectiveness outcomes

Mortality

Among hospitalized patients, pooled results from nine RCTs (N=12,639) showed that remdesivir had slight benefit on all-cause mortality at day 28 (RR 0.90, 95% CI 0.83-0.98; I²=0%). Sensitivity analysis excluding the studies with very serious risk of bias showed similar results (RR 0.90, 95% CI 0.83-0.98; I²=0%).

Subgroup analysis: Disease severity

Subgroup analysis by disease severity at baseline showed no significant benefit among patients with mildmoderate disease (RR 0.80, 95% CI 0.55-1.17; $I^2=0\%$). There was a trend towards benefit in reducing mortality among patients with severe disease (RR 0.61, 95% CI 0.35-1.07); however, there was significant heterogeneity ($I^2=61\%$). There was no significant difference in mortality among patients with critical disease (RR 0.96, 95% CI 0.87-1.04; $I^2=0\%$).

A sensitivity analysis was done where patients on low/high flow oxygen from the WHO Solidarity Trial were included in the severe subgroup instead of the critical subgroup. Results similarly showed no significant benefit among patients with mild-moderate disease (RR 0.80, 95% CI 0.55-1.17; $I^2=0\%$), and a trend towards benefit in reducing mortality among patients with severe disease (RR 0.72, 95% CI 0.50-1.03); however, there was significant heterogeneity for the severe disease subgroup ($I^2=67\%$). There was no significant difference in mortality in the critical disease subgroup (RR 1.03, 95% CI 0.90-1.18; $I^2=0\%$).

Subgroup analysis: Oxygen requirement

Subgroup analysis by oxygen requirement at baseline showed no significant benefit among patients without oxygen requirement (RR 0.80, 95% CI 0.55-1.17; $I^2=0\%$). There was a trend towards benefit in reducing mortality among patients on low flow oxygen (RR 0.61, 95% CI 0.35-1.07, $I^2=61\%$) and on high flow oxygen (RR 0.90, 95% CI 0.80-1.00 $I^2=0\%$). Result on low flow oxygen significant heterogeneity. There was a trend towards harm for those on mechanical ventilation (RR 1.06, 95% CI 0.92-1.23; $I^2=0\%$). However, the wide confidence interval in all subgroups precluded definite conclusions to be made.

Subgroup analysis: Treatment duration

Subgroup analysis by treatment duration showed inconclusive effect on mortality for those given a 5-day course of remdesivir (RR 0.98, 95% CI 0.37-2.56; $l^2=0\%$). There was a slight benefit on mortality among those given a 10-day course (RR 0.90, 95% CI 0.83- 0.98; $l^2=0\%$)

Other Outcomes

Four RCTs contributed data for clinical improvement. Pooled analysis showed that remdesivir has marginal benefit on clinical improvement up to day 28 (RR 1.07, 95% CI 1.01-1.13; $I^2=0\%$). Remdesivir may decrease clinical deterioration as measured by the WHO progression scale (RR 0.75, 95% CI 0.62-0.89; $I^2=0\%$). However, no significant effect was seen on time to clinical improvement (RR 1.07, 95% CI 0.91-1.27; $I^2=50.7\%$), with moderate heterogeneity.

Remdesivir has a small benefit in recovery rate (Rate ratio 1.22, 95% CI 1.11-1.35, I²=0%). On subgroup analysis according to baseline oxygen requirement, there was significant benefit in recovery rate among patients with severe COVID-19 requiring low flow oxygen support (RR 1.45, 95% CI 1.18-1.79). There was no significant benefit for patients not receiving oxygen support (RR 1.16, 95% CI 0.96-1.38), those on high flow oxygen or non-invasive mechanical ventilation (Rate ratio 1.09, 95% CI 0.76-1.57) and on mechanical ventilation or ECMO (Rate ratio 0.98, 95% CI 0.70-1.37).



There was significant reduction in the need for mechanical ventilation among patients given remdesivir (RR 0.72, 95% CI 0.55-0.94); however, there was significant heterogeneity (I²=76%). There was inconclusive effect in the need for ICU admission (RR 0.98, 95% CI 0.43-2.22; 1 RCT, 181 participants).

Non-hospitalized patients

Among non-hospitalized patients, one RCT (N=562) showed that a 3-day course of remdesivir within 7 days of symptom onset reduced risk of COVID-19 related hospitalization (RR 0.13, 95% CI 0.03-0.59), all cause-hospitalization (RR 0.28, 95% CI 0.10-0.75) and COVID-related medically attended visit (RR 0.19, 95% CI 0.07-0.56) by day 28 compared to placebo. Alleviation of symptoms by day 14 using FLU-PRO Plus questionnaire was inconclusive (RR 1.41, 95% CI 0.73-2.69). None of the patients in both groups died by day 28.

Appendix 5 contains the forest plots for these outcomes.

Safety outcomes

A total of five RCTs (N=4,033) contributed data to the pooled analysis on adverse events among hospitalized patients. Compared to control, patients given remdesivir had no difference in their risk for adverse events (RR 0.99, 95% CI 0.92-1.08; I²=31%). There was no significant benefit on serious adverse events (RR 0.84, 95% CI 0.65-1.09; I²=62%).

Among outpatients (1 RCT, N=562), there was no significant difference in adverse events between groups (RR 0.90, 95% CI 0.75-1.09). However, there was a reduced risk of serious adverse events in the remdesivir group (RR 0.26, 95% CI 0.10-0.70).

Common adverse events were pyrexia, rash, anemia, decreased lymphocyte count, increased neutrophil count, hyperglycemia, increased creatinine level, hypoalbuminemia, and decreased glomerular filtration rate. Other adverse events reported include hypersensitivity reactions (angioedema, rash), seizures, and elevations in hepatic enzymes. Serious adverse events reported in both groups were respiratory failure, cardiopulmonary failure, and renal failure necessitating renal replacement therapy.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of recommendations from other groups

Regulatory Agency	Recommendation	Strength of Recommendation / Certainty of Evidence
World Health Organization	We suggest treatment with remdesivir for patients with	Conditional
(WHO)	non-severe COVID-19 at highest risk of hospitalization	recommendation
(as of September 16, 2022)	We suggest treatment with remdesivir for patients with	Conditional
[19]	severe COVID-19	recommendation
	We suggest not to use remdesivir for patients with critical	Conditional
	COVID-19	recommendation
		against
Infectious Diseases Society	Among patients (ambulatory or hospitalized) with mild-to-	Conditional
of America (IDSA)	moderate COVID-19 at high risk for progression to	recommendation,
(as of August 30, 2022)	severe disease, the IDSA guideline panel suggests	Low certainty of
[20]	remdesivir initiated within seven days of symptom onset	evidence
	rather than no remdesivir.	
	In patients on supplemental oxygen but not on	Conditional
	mechanical ventilation or ECMO, the IDSA panel	recommendation,
	suggests treatment with five days of remdesivir rather	Low certainty of
	than 10 days of remdesivir.	evidence
	In hospitalized patients with severe* COVID-19, the	Conditional
	IDSA panel	recommendation,
	suggests remdesivir over no antiviral treatment.	Moderate certainty of evidence



	*Sovere illeges is defined as patients with SpO2 <0.4%	1
	on room air	
	Suggest against the routine initiation of remdesivir in patients on invasive ventilation and/or ECMO.	Conditional recommendation, Very low certainty of evidence
US National Institutes of Health (NIH) (as of August 8, 2022) [21]	The Panel recommends using remdesivir for the treatment of COVID-19 in patients who do not require supplemental oxygen and who are at high risk of progressing to severe disease (Moderate recommendation).	Moderate recommendation
	For patients with COVID-19 who only require minimal conventional oxygen, the Panel recommends using remdesivir without dexamethasone.	Moderate recommendation
	For most patients with COVID-19 who require conventional oxygen, the Panel recommends using dexamethasone plus remdesivir.	Moderate recommendation
	For hospitalized patients who require HFNC oxygen or NIV and have certain medical conditions, the Panel recommends adding remdesivir to 1 of the recommended immunomodulator combinations.	Weak recommendation
	The Panel recommends against the use of remdesivir without immunomodulators in hospitalized patients who require HFNC oxygen or NIV.	Strong recommendation
	The Panel recommends remdesivir, with or without dexamethasone, for hospitalized children who have a new or increasing need for conventional oxygen, and recommends remdesivir in combination with dexamethasone for children who require oxygen through a high-flow device or NIV	Moderate recommendation
	For children hospitalized for COVID-19 who do not require supplemental oxygen, the Panel recommends remdesivir for children aged 12 to 17 years who are at the highest risk for progression to severe disease.	Weak recommendation
	There is insufficient evidence for or against the use of remdesivir in hospitalized children aged 28 days to <12 years and weighing ≥3kg who do not require supplemental oxygen.	
	Remdesivir, as an alternative to ritonavir-boosted nirmatrelvir, can be considered for children aged ≥12 years who are at the highest risk of progression to severe COVID-19.	Weak recommendation
	For nonhospitalized children aged <12 years who are at the highest risk of progression to severe disease and for children who are at intermediate risk of severe disease, there is insufficient evidence to recommend either for or against the routine use of remdesivir for the treatment of COVID-19.	
Australian COVID-19 Treatment Guidelines (As September 19, 2022) [22]	Consider using remdesivir in adults with COVID-19 who require oxygen but do not require invasive or non-invasive ventilation.	Conditional recommendation
	Do not start remdesivir in adults hospitalized with COVID-19 who require non-invasive or invasive ventilation.	
	Consider using remdesivir within 7 days of symptom onset in unvaccinated adults with COVID-19 who do not require oxygen and who have one or more risk factors* for disease progression.	Conditional recommendation
	*Risk factors for disease progression include the following:	



 Age ≥60 years Diabetes Obesity (BMI ≥30kg/m²) Chronic kidney disease (any stage) Cardiovascular or cerebrovascular disease (coronary artery disease, congenital heart disease, heart failure, cardiomyopathy, or history of stroke) Hypertension (systemic or pulmonary) Chronic liver disease Chronic lung disease (chronic obstructive pulmonary disease, moderate-severe asthma, cystic or pulmonary fibrosis) Sickle cell disease Current cancer Immunocompromised state 	
In addition to at-risk unvaccinated adults, also consider using remdesivir within 7 days of symptom onset in adults with COVID-19 who do not require oxygen and: are immunocompromised regardless of vaccination status; or who are not up-to-date with vaccination and who are at high risk of severe disease on the basis of age and multiple risk factors.	Consensus recommendation
Consider using, in exceptional circumstances, remdesivir for the treatment of COVID-19 within 7 days of symptom onset in children and adolescents aged 28 days and over and weighing at least 3 kg who do not require oxygen and are at high risk of deterioration, where other treatments are not available / appropriate.	Consensus recommendation
Consider using remdesivir in eligible children and adolescents who have not received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, those who are immunocompromised regardless of vaccination / previous infection status, or those who are not eligible for vaccination based on age but who are at high risk of disease progression. Do not routinely use remdesivir in children and adolescents who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months unless immunocompromised.	Consensus recommendation

RESEARCH GAPS

As of September 4, 2022, there are 33 registered trials on remdesivir. These upcoming and ongoing trials include trials among adolescents, children, pregnant women, outpatients, and patients with chronic kidney disease (see Appendix 6).

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

Remdesivir is available in the Philippines as 100mg of lyophilized powder for reconstitution in a single-use vial, under a compassionate special permit (CSP) for use in the treatment of COVID-19 [17]. The suggested retail price specified in a DOH memorandum is up to ₱8,200 per 100mg vial [18]. Using the dosing of 200mg IV on Day 1 and 100mg IV on Days 2 to 10 for a 10-day course, the total cost per patient (at the SRP) is ₱90,200.00.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Remdesivir has been granted emergency use authorization by the US FDA for the treatment of COVID-19 in adults and children aged \geq 28 days and weighing \geq 3kg.



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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=8/10)

FACTORS			RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS				
Problem	No	Yes (8)					 Yes, COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large (2)	Moderate (2)	Small (2)	Trivial	Varies (2)	Uncertain	 Among hospitalized patients, remdesivir had slight benefit on all-cause mortality at day 28 (RR 0.90, 95% CI 0.83, 0.98; I2 = 0%), with trend towards mortality reduction among patients on low-flow oxygen supplementation and on high flow oxygen. Remdesivir has marginal benefit on clinical improvement up to Day 28 (RR 1.07, 95% CI 1.01 - 1.13). Remdesivir may decrease clinical deterioration as measured by the WHO progression scale (RR 0.75, 95% CI 0.62, 0.89) and need for mechanical ventilation (RR 0.72, 95% CI 0.55, 0.94). Among non-hospitalized patients, a 3-day course of remdesivir within 7 days of symptom onset reduced risk of COVID-19 related hospitalization (RR 0.13, 95% CI 0.03, 0.59), all cause-hospitalization (RR 0.28, 95% CI 0.07, 0.56) by day 28 compared to placebo. Alleviation of symptoms by day 14 using FLU-PRO Plus questionnaire was inconclusive (RR 1.41, 95% CI 0.73, 2.69). None of the patients in both groups died by day 28.



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Harm	Large	Moderate (3)	Small (4)	Trivial	Varies (1)	Uncertain	 Among hospitalized patients, remdesivir showed no effect on adverse events of any grade (RR 0.99, 95% Cl 0.92 - 1.08) and no significant difference in serious adverse events (RR 0.84, 95% Cl 0.65 - 1.09). Among non-hospitalized patients, remdesivir had no significant effect on adverse events (RR 0.90, 95% Cl 0.75,1.09) but was associated with a reduced risk of serious adverse events (RR 0.26, 95% Cl 0.10-0.70).
Certainty of Evidence	High	Moderate (8)	Low	Very low			• The overall certainty of evidence was low due to serious risk of bias AND inconsistency or imprecision in several critical outcomes. The serious risk of bias was due to concerns in selection, performance bias, detection bias, attrition bias, and reporting bias in most of the included studies.
Balance of effects	Favors intervention (1)	Probably favors intervention (6)	Does not favor intervention	Probably favors no intervention	Favors no intervention	Varies (1)	 Net potential benefit for outpatients with mild to moderate COVID-19 infection with at least 1 risk factor for progression to severe disease. Among hospitalized patients, remdesivir may have potential benefit for patients requiring low flow or high flow O2 supplementation, but net potential harm for patients requiring mechanical ventilation.
Values	Important uncertainty or variability	Possibly important uncertainty or variability (5)	Probably no important uncertainty or variability (3)	No important uncertainty or variability			No research evidence
Resources Required	Uncertain	Large costs (6)	Moderate costs (2)	Negligible cost or savings	Moderate savings	Large savings	 Remdesivir is available in the Philippines as 100 mg of lyophilized powder for reconstitution in a single- use vial, under a compassionate



							 special permit (CSP) for use in the treatment of COVID-19. The suggested retail price specified in a DOH memorandum is up to PhP 8,200 per 100 mg vial. However, there have been reports of remdesivir being sold at up to PhP 30,000 per 100 mg vial. Using the dosing of 200 mg IV on Day 1 and 100 mg IV on Days 2 - 10 for a 10 day course, the total cost per patient (at the SRP) is PhP 90,200.00. Remdesivir has been granted emergency use authorization by the US FDA for the treatment of COVID-19 in adults and children.
Certainty of evidence of required resources	No included studies (1)	Very low (2)	Low (2)	Moderate (2)	High (1)		 The suggested retail price is from a DOH memorandum.
Cost effectiveness	No included studies (4)	Favors using the comparison (1)	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the invention (2)	Favors the intervention (1)	No research evidence
Equity	Uncertain	Varies (3)	Probably reduced (1)	Reduced (1)	Probably increased (2)	Increased (1)	No research evidence
Acceptability	Uncertain	Varies (4)	No	Probably no (1)	Probably yes (3)	Yes	
Feasibility	Uncertain	Varies (3)	No	Probably no (1)	Probably yes (4)	Yes	



Appendix 2: Search Strategy and Results

	SEARCH STRATEGY /	DATE AND TIME	RESULTS		
DATABASE	SEARCH TERMS	OF SEARCH	Yield	Eligible	
Medline https://pubmed.ncbi. nlm.nih.gov/	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir) Filters: January 01, 2022 to September 4, 2022	4 September 2022, 1500	387	1	
CENTRAL https://www.cochran elibrary.com/1dvanc ed-search	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir) Filters: January 2022 to September 4, 2022	4 September 2022, 1500	87	1	
COVID-NMA initiative https://covid- nma.com/	(remdesivir)	4 September 2022, 1500	14	0	
Ongoing trials					
ClinicalTrials.gov https://clinicaltrials.g ov/	covid19 OR covid 19 OR covid- 19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir)	4 September 2022, 1500	118	32	
Chinese Clinical Trial Registry http://www.chictr.org .cn/searchprojen.asp x	remdesivir	4 September 2022, 1500	0	0	



EU Clinical Trials Register https://www.clinicaltri alsregister.eu/	covid 19 AND remdesivir	4 September 2022, 1500	3	1
Republic of Korea – Clinical Research Information Service https://cris.nih.go.kr/ cris/info/introduce.do ?search_lang=E&lan g=E	remdesivir	4 September 2022, 1500	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search https://rctportal.niph. go.jp/en/	remdesivir	4 September 2022, 1500	8	0
CenterWatch https://www.centerw atch.com/clinical- trials/listings/	remdesivir	4 September 2022, 1500	20	2
Preprints				
chinaxiv.org	remdesivir	4 September 2022, 1500	0	0
Medrxiv.org	Remdesivir Filters: January to September 4, 2022	4 September 2022, 1500	201	0
Biorxiv.org	Remdesivir Filters: January to September 4, 2022	4 September 2022, 1500	83	0



Appendix 3: Characteristics of Included Studies

Title/ Author	Country	Number of patients	Population	Intervention group(s)	Control	Outcome/s
Wang, 2020 [6]	China	237 randomized, 226 evaluated	Severe COVID-19 patients Follow-up time: up to Day 28	Remdesivir 200 mg IV on D1, followed by 100 mg IV on D2 – D10	Placebo	Clinical status (6- point ordinal scale) Clinical improvement (2 points reduction from baseline, or discharge from hospital) Time to clinical improvement Viral load Mortality Adverse events
WHO Solidarity Consortium, 2022 [7]	Europe Canada Latin America Asia Africa	14,221 total randomized 8,275 allocated 1:1 to remdesivir and control	Patients hospitalized with COVID-19 Follow-up time: up to Day 60	Remdesivir 200 mg IV on D1, followed by 100mg IV on D2 – D10 Other arms: Lopiravir/Ritonavir Hydroxychloroquine Interferon beta 1a	Standard of care	Mortality Use of mechanical ventilation Duration of hospitalization
Beigel, 2020 [8]	USA Denmark UK, Greece Germany Korea Mexico Spain Japan Singapore	1062 randomized, 1048 evaluated	Severe COVID-19 patients Follow-up time: up to Day 29	Remdesivir 200 mg IV on D1, followed by 100 mg IV on D2 – D10	Placebo	Clinical status (using 8-category ordinal scale) Time to recovery (1- 2 category change from baseline) Mortality Adverse events
Ader, 2021 [9] Ader 2022 (Final	Austria Belgium France	857 randomized, 843 evaluated	Hospitalized COVID-19 patients requiring oxygen	Remdesivir 200 mg IV on D1, followed by 100mg	Standard of care	Clinical status on day 15 Viral load



results) [16]	Luxembourg Portugal		and/or ventilatory support Follow-up time: up to Day 90	IV on D2 – D10		Mortality Adverse events
Mahajan, 2021 [10]	India	82 randomized, 70 evaluated	Moderate to severe COVID-19 Follow-up time: up to Day 24	Remdesivir 200 mg IV on D1, followed by 100 mg on D2- D5	Standard of care	Clinical status on day 12 (6-point ordinal scale) Mortality Safety outcomes (liver and renal function tests)
Spinner, 2020 [11]	USA Europe UK Asia	596 randomized, 584 evaluated	Hospitalized patients with moderate COVID-19 Follow-up time: up to Day 28	Remdesivir 200 mg IV on D1, followed by 100 mg IV on D2 – D10 Remdesivir 200 mg IV on D1, followed by 100 mg on D2- D5	Standard of care	Clinical status on day 11 (7-point ordinal scale) Clinical improvement (2- category change from baseline) Time to recovery Adverse events
Barratt-Due, 2021 [12]	Norway	101 randomized, 83 completed 3 month follow up	Hospitalized adults with COVID-19 Follow-up time: up to Day 90	Remdesivir 200 mg IV on D1, followed by 100mg IV on D2 – D10	Standard of care	Mortality Need for mechanical ventilation ICU admission Viral load Adverse events
Abd-Elsalam, 2021 [13]	Egypt	209 randomized, 200 evaluated	Hospitalized mild to moderate patients Follow-up time: up to Day 28	Remdesivir 200 mg IV on D1, followed by 100mg IV on D2 – D10	Standard of care	Length of hospital stay Need for mechanical ventilation Adverse events
Gottlieb, 2021 [14]	United States Spain Denmark	584 randomized, 562 evaluated	Non-hospitalized patients with mild to moderate COVID-19	Remdesivir 200 mg IV on D1, followed by 100mg	Placebo	COVID-19 related hospitalization or death from any



	United Kingdom		with risk factors for progression to severe disease within 7 days of symptom onset Follow-up time: Up to Day 28	IV on D2 – D3		cause by Day 28 COVID-19 related medically attended visit or death from any cause by Day 28 Adverse events
Ali, 2022 [15]	Canada	1,282 randomized, 1,281 analyzed	Hospitalized patients with laboratory confirmed SARS-CoV-2 infection Follow up: 28 days	Remdesivir 200 mg IV on D0, followed by 100 mg IV on Day 1-9	Standard of care	Mortality, need for mechanical ventilation, hospital length of stay, clinical severity of illness (WHO ordinal scale), adverse events (hepatic dysfunction and need for renal replacement therapy)



Institute of Clinical Epidemiology, National Institutes of Health, UP Manila In cooperation with the Philippine Society for Microbiology and Infectious Diseases Funded by the Department of Health

Appendix 4: Detailed Study Appraisal



Figure 1. Detailed Study Appraisal



Appendix 5: GRADE Evidence Profile

Author(s): Carol Stephanie C. Tan Lim, MD, MSc

Question: Remdesivir compared to Placebo/Standard Care for COVID-19 hospitalized adult patients

			Certainty a	ssessment			N≌ (of patients		Effect	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Placebo/Standard Care	Relative (95% Cl)	Absolute (95% Cl)		
Mortality	/ (Day 28)											
9	randomised trials	seriousª	not serious	not serious	serious⁵	none	855/6452 (13.3%)	931/6187 (15.0%)	RR 0.90 (0.83- 0.98)	15 fewer per 1,000 (from 26 fewer to 3 fewer)	⊕⊕⊖⊖ Low	CRITICAL
Clinical	improvement											
4	randomised trials	serious⁰	not serious	not serious	serious ^b	none	715/1024 (69.8%)	455/748 (60.8%)	RR 1.07 (1.01-1.13)	43 more per 1,000 (from 6 more to 79 more)	⊕⊕⊖⊖ Low	CRITICAL
Clinical	deterioration											
5	randomised trials	serious	not serious	not serious	not serious	none	189/1565 (12.1%)	229/1269 (18.0%)	RR 0.75 (0.62-0.89)	45 fewer per 1,000 (from 69 fewer to 20 fewer)	⊕⊕⊕⊖ Moderate	CRITICAL
Need for	r mechanical v	entilation										
5	randomised trials	seriousd	seriouse	not serious	not serious	none	704/5262 (13.4%)	859/5237 (16.4%)	RR 0.72 (0.55-0.94)	46 fewer per 1,000 (from 74 fewer to 10 fewer)	⊕⊕⊖⊖ Low	CRITICAL
Serious	adverse event	s					•				•	
5	randomised trials	serious ^f	not serious	not serious	serious ^g	none	341/2139 (15.9%)	354/1870 (18.9%)	RR 0.84 (0.65-1.09)	30 fewer per 1,000 (from 66 fewer to 17 more)	⊕⊕⊖⊖ Low	CRITICAL
Adverse	events											
5	randomised trials	serious ^f	not serious	not serious	not serious	none	941/2158 (43.6%)	790/1875 (42.1%)	RR 0.99 (0.92-1.08)	4 fewer per 1,000 (from 34 fewer to 34 more)	⊕⊕⊕⊖ Moderate	IMPORTANT
							•				•	

Explanations

a. Issues with randomization, performance bias, detection bias, missing outcome data, and reporting bias in majority of studies

b. Upper or lower limit of confidence interval near no-effect value

c. 1 study with high risk of bias, the rest with overall some concerns for bias

d. 4 studies with overall some concerns for bias due to issues with deviation from intended intervention (2 studies), missing outcome data (1 study), outcome measurement bias (3 studies) and reporting bias (2 studies)

e. Significant heterogeneity

f. All studies with some concern for bias due to issues with deviation from intended intervention, missing outcome data, outcome measurement bias and reporting bias

g. Wide confidence interval



Author(s): Mary Christine Castro, MD,MSc, Carol Stephanie C. Tan Lim, MD, MSc Question: Remdesivir compared to Placebo/Standard Care for non-hospitalized adult patients with COVID-19

			Certainty asse	ssment			Nº of p	atients		Effect	l.	
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	placebo or standard of care	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance

COVID-related hospitalization

1	randomised trial	not serious	not serious	not serious	Seriousª	none	2/279 (0.7%)	15/283 (5.3%)	RR 0.13 (0.03-0.59)	46 fewer per 1,000 (from 51 fewer to 32 fewer)	⊕⊕⊕⊖ Moderate	CRITICAL
										,		

COVID-related medically attended visits by Day 28

1	randomised trial	not serious	not serious	not serious	Seriousª	none	4/246 (1.6%)	21/252 (8.3%)	RR 0.19 (0.07-0.56)	68 fewer per	⊕⊕⊕⊖ Moderate	IMPORTANT
										1,000 (from 77 fewer to 37 fewer)		

All-cause hospitalization by Day 28

1	randomised trials	not serious	not serious	not serious	Seriousª	none	5/279 (1.8%)	18/283 (6.4%)	RR 0.28 (0.10-0.75)	46 fewer per 1,000 (from 57 fewer to 16 fewer)	⊕⊕⊕⊖ Moderate	CRITICAL
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Alleviation of symptoms by Day 14

1	randomised trials	not serious	not serious	not serious	Serious ^b	none	23/66 (34.8%)	15/60 (25.0%)	RR 1.41 (0.73-2.69)	102 more per 1,000 (from 68 fewer to 423 more)	⊕⊕⊕⊖ Moderate	IMPORTANT



Adverse events

1	randomised trials	not serious	not serious	not serious	Serious ^b	none	118/279 (42.3%)	131/283 (46.3%)	RR 0.90 (0.75-1.09)	46 fewer per 1,000 (from 116 fewer to 42 more)	⊕⊕⊕⊖ Moderate	IMPORTANT

Serious adverse events

1	randomised trials	not serious	not serious	not serious	Seriousª	none	5/279 (1.8%)	19/283 (6.7%)	RR 0.26 (0.10-0.70)	50 fewer per 1,000 (from 60 fewer to 20 fewer)	⊕⊕⊕⊖ Moderate	CRITICAL
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CI: confidence interval; HR: hazard Ratio; RR: risk ratio

Explanations

a. Study did not reach target sample size due to administrative reasons, small number of events not reaching optimal information size b. Wide confidence interval



Author(s): Carol Stephanie C. Tan Lim, MD, MSc

Question: Remdesivir compared to Placebo/Standard Care for COVID-19 hospitalized pediatric patients

№ of studies Study design Risk of bias Inconsistency Indirectness Imprecision Other considerations Remdesivir Placebo/Standard Care Relative (95% Cl) Abs (95 Mortality (Day 28) 9 randomised trials serious ^a not serious serious ^b serious ^c none 855/6452 (13.3%) 931/6187 (15.0%) RR 0.90 (0.83-0.98) 15 fewer (from 26 fewer Clinical improvement exclusive exclusive exclusive 245/64024 455/742 (20.0%) DD 4.02 12 mone	olute % CI) per 1,000 er to 3 fewer) ⊕○○○ Very low	CRITICAL
Mortality (Day 28) 9 randomised trials serious ^a not serious ^b serious ^c none 855/6452 (13.3%) 931/6187 (15.0%) RR 0.90 (0.83-0.98) 15 fewe (from 26 few Clinical improvement	per 1,000 er to 3 fewer) ⊕⊖⊖⊂ Very low	CRITICAL
9 randomised trials serious ^a not serious serious ^b serious ^c none 855/6452 (13.3%) 931/6187 (15.0%) RR 0.90 (0.83-0.98) 15 fewe (from 26 few (from 26 few concerns)) Clinical improvement	per 1,000 er to 3 fewer) ⊕⊖⊖⊂ Very low) CRITICAL
Clinical improvement		
4 randomised serious not serious serious serious serious none (15/1024 455/748 (60.8%) (1.01-1.13) (from 6 more	per 1,000 e to 79 more) ⊕⊖⊖⊂ Very low	CRITICAL
Clinical deterioration	·	
5randomised trialsseriousdnot seriousnot seriousnot seriousnone189/1565 (12.1%)229/1269 (18.0%)RR 0.75 (0.62-0.89)45 fewer (from 69 few	per 1,000 er to 20 fewer) ⊕⊕⊖⊂ Low	CRITICAL
Need for mechanical ventilation	·	,
5randomised trialsserious ^a serious ^b not seriousnone704/5262 (13.4%) $859/5237$ (16.4%) RR 0.72 (0.55-0.94) 46 fewe (from 74 few (from 74 few)	per 1,000 er to 10 fewer) ⊕⊖⊖⊖⊂ Very low	CRITICAL
Serious adverse events	·	
5randomised trialsserious ^a not seriousserious ^b serious ^b none341/2139 (15.9%)354/1870 (18.9%)RR 0.84 (0.65-1.09)30 fewer (from 66 few	per 1,000 ⊕○○○ er to 17 more) Very low	CRITICAL
Adverse events		
5randomised trialsseriousnot seriousnot seriousnot seriousnone $941/2158$ (43.6%) $790/1875$ (42.1%) RR 0.99 ($0.92-1.08$) 4 fewer (from 34 fewer	per 1,000 ⊕⊕⊖⊂ Low	IMPORTANT

Explanations

a. Issues with randomization, performance bias, detection bias, missing outcome data, and reporting bias in majority of studies

b. Studies done on adults

c. Upper or lower limit of confidence interval near no-effect value

d. 1 study with high risk of bias, the rest with overall some concerns for bias

e. 4 studies with overall some concerns for bias due to issues with deviation from intended intervention (2 studies), missing outcome data (1 study), outcome measurement bias (3 studies) and reporting bias (2 studies)

f. Significant heterogeneity

g. All studies with some concern for bias due to issues with deviation from intended intervention, missing outcome data, outcome measurement bias and reporting bias

h. Wide confidence interval



Author(s): Carol Stephanie C. Tan Lim, MD, MSc

Question: Remdesivir compared to Placebo/Standard Care for non-hospitalized pediatric patients with COVID-19

			Certainty asse	essment			Nº of p	atients		Effect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	placebo or standard of care	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance

COVID-related hospitalization

1	randomised trial	not serious	not serious	seriousª	Serious ^b	none	2/279 (0.7%)	15/283 (5.3%)	RR 0.13 (0.03-0.59)	46 fewer per 1,000 (from 51 fewer to 32 fewer)	⊕⊕⊖⊖ Low	CRITICAL

COVID-related medically attended visits by Day 28

1	randomised trial	not serious	not serious	seriousª	Serious ^b	none	4/246 (1.6%)	21/252 (8.3%)	RR 0.19 (0.07-0.56)	68 fewer per	⊕⊕⊖⊖ Low	IMPORTANT
										1,000 (from 77 fewer to 37 fewer)		

All-cause hospitalization by Day 28

1	randomised trials	not serious	not serious	seriousª	Serious ^b	none	5/279 (1.8%)	18/283 (6.4%)	RR 0.28 (0.10-0.75)	46 fewer per 1,000 (from 57 fewer to 16 fewer)	⊕⊕⊖⊖ Low	CRITICAL
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Alleviation of symptoms by Day 14



	1	randomised trials	not serious	not serious	seriousª	Serious°	none	23/66 (34.8%)	15/60 (25.0%)	RR 1.41 (0.73-2.69)	102 more per 1,000 (from 68 fewer to 423 more)	⊕⊕⊖⊖ Low	IMPORTANT
I													

Adverse events

1	randomised trials	not serious	not serious	seriousª	Serious ^c	none	118/279 (42.3%)	131/283 (46.3%)	RR 0.90 (0.75-1.09)	46 fewer per 1,000 (from 116 fewer to 42 more)	⊕⊕⊖⊖ Low	IMPORTANT

Serious adverse events

1	randomised trials	not serious	not serious	seriousª	Serious ^b	none	5/279 (1.8%)	19/283 (6.7%)	RR 0.26 (0.10-0.70)	50 fewer per 1,000 (from 60 fewer to 20 fewer)	⊕⊕⊖⊖ Low	CRITICAL
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CI: confidence interval; HR: hazard Ratio; RR: risk ratio

Explanations

a. Study included only 8 patients aged 12-18 years old
b. Study did not reach target sample size due to administrative reasons, small number of events not reaching optimal information size
c. Wide confidence interval



Appendix 6: Forest Plots

	Remde	sivir	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Abd-Elsalam 2021	9	100	7	100	0.8%	1.29 [0.50, 3.32]	I
Ader 2021	34	414	37	418	3.7%	0.93 [0.59, 1.45]	I —∎—
Ali 2022	117	625	145	642	15.6%	0.83 [0.67, 1.03]	
Barratt-Due 2021	1	43	3	58	0.1%	0.45 [0.05, 4.18]	I
Belgel 2020	59	541	77	521	7.3%	0.74 [0.54, 1.01]	I
Mahajan 2021	6	41	5	41	0.6%	1.20 [0.40, 3.62]	I —
Spinner 2020	5	364	4	200	0.4%	0.65 [0.18, 2.40]	I — — — — — — — — — — — — — — — — — — —
Wang 2020	22	158	10	78	1.5%	1.09 [0.54, 2.18]	I — —
WHO 2022	602	4146	643	4129	69.9%	0.93 [0.84, 1.03]	· •
Total (95% CI)		6452		6187	100.0%	0.90 [0.83, 0.98]	1 🔶
Total events	855		931				
Heterogeneity: Tau ² =	0.00; Cl	$h^2 = 4.3$	22, df =	8 (P =	0.84); f ² •	- 0%	
Test for overall effect:	Z = 2.33	l (P = 0	.02)	-			Favours Remdesivir Favours Control



	Remde	sivir	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
Abd-Elsalam 2021	9	100	7	100	0.6%	1.29 [0.50, 3.32]	
Ader 2021	34	414	37	418	3.7%	0.93 [0.59, 1.45]	
Ali 2022	117	625	145	642	15.6X	0.83 [0.67, 1.03]	
Barratt-Due 2021	1	43	3	58	0.1%	0.45 [0.05, 4.18]	
Belgel 2020	59	541	77	521	7.3%	0.74 [0.54, 1.01]	
Spinner 2020	5	384	4	200	0.4%	0.65 [0.18, 2.40]	
Wang 2020	22	158	10	78	1.5%	1.09 [0.54, 2.18]	
WHO 2022	602	4146	643	4129	70.4%	0.93 [0.84, 1.03]	-
Total (95% CI)		6411		6146	100.0%	0.90 [0.83, 0.98]	•
Total events	649		926				-
Heterogeneity: Tau ² =	0.00; Cl	$1^2 = 3.9$	97, df =	7 (P =	0.78); l ² =	- 0%	
Test for overall effect:	Z = 2.36	i (P = 0	.02)	-			Favours Remdesivir Favours Control

Figure 2a. Pooled effect of remdesivir on all-cause mortality at Day 28 among hospitalized patients (sensitivity analysis excluding studies with very serious risk of bias)



	Remde	sivir	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.2.1 Mild-moderate							
Abd-Elsalam (No O2) 2021	9	100	7	100	1.6%	1.29 [0.50, 3.32]	
All (No O2) 2022	7	68	6	54	1.6%	0.69 [0.27, 1.80]	
Beigel (No O2) 2020	3	75	3	63	0.6%	0.64 [0.16, 4.02]	· · · · · · · · · · · · · · · · · · ·
Spinner (No O2) 2020	5	384	4	200	0.9%	0.65 [0.18, 2.40]	
WHO (No O2) 2022	25	869	33	861	4.9%	0.75 [0.45, 1.25]	
Subtotal (95% CI)		1496		1278	9.5%	0.80 [0.55, 1.17]	
Total events	49		55				
Heterogeneity: Tau ² = 0.00; Cl	nt ² = 1.21	, df = 4	P = 0.1	88); I ² -	0%		
Test for overall effect: Z = 1.14	$(\mathbf{P}=0.2)$	5)					
1.2.2 Severe							
Ader (No/low flow) 2021	15	253	15	251	2.6%	0.99 [0.50, 1.99]	
All (Low flow) 2022	36	330	58	360	7.7%	0.68 [0.46, 1.00]	
Bekgel (Low flow) 2020	9	232	25	203	2.5%	0.32 [0.15, 0.66]	
Subtotal (95% CI)	-	815	-	814	13.1%	0.61 [0.35, 1.07]	
Total events	60		98				
Heterogeneity: Tau ² = 0.15; Cl	1 ² = 5.17	, df = 2	P = 0.0	08); f ² =	61%		
Test for overall effect: Z = 1.73	$\langle P = 0.0 \rangle$	6)	•				
1.2.3 Critical							
Ader (High flow/NIV/IV) 2021	19	161	22	167	4.0%	0.90 [0.50, 1.59]	
All (High flow) 2022	45	149	52	153	9.9%	0.89 [0.64, 1.24]	
Ali (N) 2022	19	56	21	52	5.2%	0.84 [0.51, 1.37]	
Ali (NIV) 2022	10	22	6	23	2.1%	1.74 [0.76, 3.98]	
Beigel (High flow/NIV) 2020	19	95	20	98	4.2%	0.98 [0.56, 1.72]	
Beigel (IV) 2020	28	131	29	154	5.8%	1.14 [0.71, 1.81]	
WHO (Low/high flow) 2022	426	2918	476	2921	26.2%	0.90 [0.79, 1.01]	
WHO (NIV/IV) 2022	151	359	134	347	20.0%	1.09 [0.91, 1.30]	- -
Subtotal (95% CI)	-	3891	-	3915	77.4%	0.96 [0.87, 1.04]	•
Total events	717		760				
Heterogeneity: Tau ² = 0.00; Ch	n ² = 6.25	, df = 7	P = 0.	51); P -	- 0%		
Test for overall effect: Z = 1.01	(P = 0.3)	1)					
Total (95% CI)		6202		6007	100.0%	0.91 [0.80, 1.02]	•
Total events	826		913				-
Heterogeneity: Tau ² = 0.01; Cl	$1^2 = 19.3$	2. df =	15 (P =	0.20);	² = 22%	-	
Test for overall effect: Z = 1.59	(P = 0.1)	1)		,			0.2 0.5 1 2 5
Test for subgroup differences:	$Cht^{2} = 3.0$)6. df =	2 (P =)	0.21). P	- 35.18	í	Favours Remdesivir Favours Control

Figure 3. Subgroup analysis for mortality by disease severity



	Downdo		C			Diala Datia	
Study or Subgroup	Evente	Total	Evente	Total	Waight	KISK KATIO	KISK KATIO
1.5.1 Mild-moderate	Lvents	Total	Events	TOTAL	weight	M-n, Kanuoni, 55% Ci	M-H, Kalldolli, 55% Cl
Abd-Ekalam (No O2) 2021	9	100	7	100	1.6%	1 29 (0 50 3 32)	
All (No O2) 2022	7	68	8	54	1.6%	0.69 [0.27, 1.80]	
Bekgel (No O2) 2020	3	75	3	63	0.6%	0.64 [0.16, 4.02]	
Spinner (No O2) 2020	5	384	4	200	0.9%	0.65 [0.18, 2.40]	
WHO (No O2) 2022	25	669	33	861	4.9%	0.75 [0.45, 1.25]	_
Subtotal (95% CI)		1496		1278	9.5%	0.80 [0.55, 1.17]	
Total events	49		55				
Heterogeneity: Tau ² = 0.00; Cl	hť = 1.21	, df = 4	4 (P = 0.	86); i² -	- 0%		
Test for overall effect: $Z = 1.14$	$(\mathbf{P}=0.2)$	5)					
1.5.2 Severe							
Ader (No/low flow) 2021	15	253	15	251	2.6%	0.99 [0.50, 1.99]	
All (Low flow) 2022	36	330	58	360	7.7%	0.68 [0.46, 1.00]	
Beigel (Low flow) 2020	9	232	25	203	2.5%	0.32 [0.15, 0.66]	
WHO (Low/high flow) 2022	426	2918	476	2921	26.2%	0.90 [0.79, 1.01]	-
Subtotal (95% CI)		3733		3735	39.3%	0.72 [0.50, 1.03]	-
Total events	466		574				
Heterogeneity: Tau ⁴ = 0.06; Cl Test for overall effect: Z = 1.76	n# = 9.19 3 (P = 0.0	, df = : 7)	s (P = 0.0	03); r •	67%		
1.5.3 Critical							
Ader (High flow/NIV/IV) 2021	19	161	22	167	4.0%	0.90 [0.50, 1.59]	
All (High flow) 2022	45	149	52	153	9.9%	0.69 [0.64, 1.24]	+
Ali (IV) 2022	19	56	21	52	5.2%	0.64 [0.51, 1.37]	
Ali (NIV) 2022	10	22	6	23	2.1%	1.74 [0.76, 3.98]	
Beigel (High flow/NIV) 2020	19	95	20	96	4.2%	0.98 [0.56, 1.72]	
Belgel (IV) 2020	26	131	29	154	5.6%	1.14 [0.71, 1.81]	_
WHO (NIV/IV) 2022	151	359	134	347	20.0%	1.09 [0.91, 1.30]	<u>+</u>
Subtotal (95% CI)		973		994	51.1%	1.03 [0.90, 1.18]	•
Total events	291		264		~ -/		
Tract for events: Laur = 0.00; Cl	nr = 3.76 ≥/n _ 0.0	, df = (2)	q = 0.1	/1); r •	- 0%		
Test for overall effect: $z = 0.46$	s (F = 0.0	3)					
Total (95% CI)		6202		6007	100.0%	0.91 [0.80, 1.02]	•
Total events	826		913				
Heterogeneity: Tau ⁴ = 0.01; Cl	hr = 19.3	2, df =	15 (P =	0.20);	r = 22%		0.1 0.2 0.5 1 2 5 10
Test for overall effect: $Z = 1.59$	P = 0.1	1)	•				Favours Remdesivir Favours Control
Test for subgroup differences:	Chi" = 4.4	15. df =	: 2 (P = I	D.11), P	= 55.17	<i>(</i>	

Figure 3a. Sensitivity analysis for the subgroup analysis for mortality by disease severity (WHO low/high flow oxygen placed in the severe subgroup)



Remdesivir Control Risk Ratio Study or Subgroup Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI 1.9.1 No oxygen requirement Image: Control oxygen requirement Image: Control oxygen requirement Image: Control oxygen requirement													
Study or Subgroup	Events	Total	Events	Total	Weiaht	M-H. Random. 95% Cl	M-H. Random. 95% Cl						
1.9.1 No oxygen requirement													
Abd-Ekalam (No O2) 2021	9	100	7	100	1.6%	1 29 10 50 3 321							
All (No ()2) 2022	ž	68	Ŕ	54	1.6%	0.69 [0.27 1.80]							
Belgel (No O2) 2020	á	75	ă.	63	0.6%	0.84 [0.18, 4.02]							
Spinner (No O2) 2020	5	384	4	200	0.9%	0.65 [0.18, 2.40]							
WHO (No O2) 2022	25	869	33	861	4.9%	0.75 [0.45, 1.25]							
Subtotal (95% CI)		1496		1278	9.5%	0.80 [0.55, 1.17]							
Total events	49		55				-						
Heterogeneity: Tau ² = 0.00; Ch	r ² = 1.21	, df = 4	I(P=0)	86); i² -	0%								
Test for overall effect: $Z = 1.14$	$(\mathbf{P}=0.2)$	5)											
1.9.2 Low flow oxygen													
Adar (No /low flow) 2021	15	253	15	251	2.8%	0.99 (0.50, 1.99)							
All (Low flow) 2022	36	330	58	360	7 7%	0.68 [0.46 1.00]							
Beigel (Low flow) 2020	Â	232	25	203	2.5%	0.32 [0.15, 0.66]							
Subtotal (95% CI)		815		814	13.1%	0.61 [0.35, 1.07]							
Total events	60		98				-						
Heterogeneity: Tau ² = 0.15; Ch	r ² = 5.17	. df = 2	P = 0.0	08); f ² =	61X								
Test for overall effect: Z = 1.73	(P = 0.0	6)	•										
1.9.3 High flow oxygen													
All (High flow) 2022	45	149	52	153	9.9%	0.69 [0.64, 1.24]	_ _						
WHQ (Low/high flow) 2022	426	2918	476	2921	26.2%	0.90 [0.79, 1.01]							
Subtotal (95% CI)		3067		3074	36.1%	0.90 [0.80, 1.00]	◆						
Total events	471		528										
Heterogeneity: Tau ² = 0.00; Ch	² = 0.00	, df = 1	P=0.1	96); 1² -	0%								
Test for overall effect: Z = 1.92	$\langle P=0.0$	5)											
1.9.4 Mechanical ventilation (r	non-inva	sive or	invasiv	e)									
Ader (High flow/NIV/IV) 2021	19	161	22	167	4.0%	0.90 [0.50, 1.59]							
All (N) 2022	19	56	21	52	5.2%	0.84 [0.51, 1.37]							
All (NIV) 2022	10	22	6	23	2.1%	1.74 [0.76, 3.96]							
Beigel (High flow/NIV) 2020	19	95	20	96	4.2%	0.98 [0.56, 1.72]	_						
Belgel (IV) 2020	28	131	29	154	5.6%	1.14 [0.71, 1.81]							
WHO (NIV/IV) 2022	151	359	134	347	20.0%	1.09 [0.91, 1.30]							
Subtotal (95% CI)		824		841	41.2%	1.06 [0.92, 1.23]	•						
Total events	246		232										
Heterogeneity: $Tau^2 = 0.00$; Ch	r = 2.82	, df = 5	i (P = 0.1)	73); ۴ -	- 0%								
Test for overall effect: $Z = 0.63$	(P = 0.4)	0)											
Total (95% CI)		6202		6007	100.0%	0.91 [0.80, 1.02]	•						
Total events	826		913										
Heterogeneity: Tau ² = 0.01; Ch	r ² = 19.3	2, df =	15 (P =	0.20);	i² = 22%	-							
Test for overall effect: Z = 1.59	$\langle P=0.1$	1)					Favours Remdesivir Favours Control						
Test for subgroup differences: (;hl² = 6.4	17, df =	· 3 (P = 0	0.09), P	ⁱ = 53.6%	i							

Figure 4. Subgroup analysis for mortality by oxygen requirement

	Remde	sivir	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
1.10.1 5 days							
Mahajan 2021	6	41	5	41	0.6%	1.20 [0.40, 3.62]	
Spinner 2020	2	191	2	100	0.2%	0.52 [0.07, 3.66]	
Subtotal (95% CI)		232		141	0.8%	0.98 [0.37, 2.56]	
Total events	6		7				
Heterogeneity: Tau2 -	= 0.00; Cl	hť = 0.	53, df =	1 (P =	0.47); i ² •	= 0%	
Test for overall effect	: Z = 0.04	I (P = 0	.97)				
1.10.2 10 days							
Abd-Elsalam 2021	9	100	7	100	0.8%	1.29 [0.50, 3.32]	
Ader 2021	34	414	37	418	3.7%	0.93 [0.59, 1.45]	
All 2022	117	625	145	642	15.6%	0.83 [0.67, 1.03]	+
Barratt-Due 2021	1	43	3	58	0.1%	0.45 [0.05, 4.18]	
Beigel 2020	59	541	77	521	7.3%	0.74 [0.54, 1.01]	
Spinner 2020	3	193	2	100	0.2%	0.78 [0.13, 4.58]	
Wang 2020	22	158	10	78	1.5%	1.09 [0.54, 2.18]	
WHO 2022	602	4146	643	4129	69.9%	0.93 [0.84, 1.03]	
Subtotal (95% CI)		6220		6046	99.2%	0.90 [0.83, 0.98]	•
Total events	847		924				
Heterogeneity: Tau ² -	= 0.00; Cl	$ht^2 = 3.2$	75, df =	7 (P = 1	0.81); P	- 0%	
Test for overall effect	: Z = 2.33	3 (P = 0	.02)				
Total (95% CI)		6452		6187	100.0%	0.90 [0.83, 0.98]	•
Total events	855		931				
Heterogeneity: Tau2 -	- 0.00; Cl	$h^2 = 4.2$	31, df =	9 (P = 1	0.69); P	- 0%	
Test for overall effect	: Z = 2.33	B (P = 0)	.02)	-			U.UI U.I I 10 100
Test for subgroup dif	ferences:	$Cht^2 = 0$	0.03, df	= 1 (P •	= 0.87), I	² = 0%	ravours remuesivii Favours Control

Figure 5. Subgroup analysis for mortality by treatment duration



Clinical improvement D28

Study	Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2			A	в	Ris C	k of I D	3ias E	Overall	Weights (%)	Risk ratio [95% CI]
Mild to severe															
Spinner CD, 2020	28	Remdesivir 100 mg* (2 arms 5 &	Standard care 10days merged)	345/396	166/200	0	-		•	•	•	•		64.98%	1.05 [0.98, 1.13]
Moderate/severe		Domdoniule	Standard agro	0/41										0.109/	0.67 (0.12.3.78)
Mild to critical	24	100 mg/day*	Standard Care	241	341				•	1		•		0.1276	0.07 [0.12, 0.10]
Ader F, 2021	28	Remdesivir	Standard care	265/429	241/428									27.89%	1.10 [0.98, 1.23]
Severe		100 mg/day													
Wang Y, 2020	28	Remdesivir 100 mg*	Placebo	103/158	45/79		-1		•	•	-	•	•	7.02%	1.14 [0.92, 1.43]
Heterogeneity: Q = 1.09, p	= 0.78; I^2 = 0.0%; τ^2 = 0.00)													
		(*different loading dose)	Total:	1024	748										
Risk of blas ratings: Low Risk of Blas Some Concerns High Risk of Blas	Risk of Bias I A: Bias due to randomizat B: Bias due to deviation to C: Bias due to missing dat	Domains: ion om intended intervention	Total events:	715	455		•								1.07 [1.01 1.13]
	D: Bias due to outcome m E: Bias due to selection of	easurement f reported result		Ir	tervention 2 better		Inte	rvention 1 bi	tter			Data s	ource: the COVI	D-NMA initiative (ht	tps://covid-nma.com/)
						0.37	1 2.72								
						R	sk natio								

Figure 6. Pooled effect of remdesivir on clinical improvement up to Day 28 among hospitalized patients (Source: https://www.covid-nma.com)

WHO progression score level 7 or above D28														
[mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death]														
Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2			A	в	Risk C	of Bia D	S E	Overall	Risk Ratio [95% Cl]	
28	Remdesivir	Standard care	6/396	8/200		+							2.86% 0.38 [0.13, 1.08]	
	Too mg (2 arms 5	a rodays merged)												
24	Remdesivir S	Standard care	10/41	7/41						-		-	4.19% 1.43 [0.60, 3.39]	
	100 mg/day*					1					- 7	-		
28	Remdesivir S 100 mg/day*	Standard care	60/429	79/428	н	•		-	-	-	-		32.94% 0.76 [0.56, 1.03]	
28	Remdesivir	Remdesivir	Placebo	89/541	122/521		•		-		-	-		51.85% 0.70 [0.55, 0.90]
	100 mg*													
28	Remdesivir 100 mg*	Placebo	24/158	13/79	F	+							8.16% 0.92 [0.50, 1.71]	
$0.34; I^2 = 0.0\%; \tau^2 = 0.00$	D													
	(*different loading dose)					1								
Risk of A: Bias due to randt B: Bias due to detwi C: Bias due to missi D: Bias due to selec E: Bias due to selec	Blas Domains: omization tion from intended interventi ing data me measurement tion of reported result	Total:	1565 189	1269 229 Intervention	l better 0.14	•	Intervention 2	bette	r.	Data	source	the COVID-NM	0.75 [0.62, 0.89] A initiative (https://covid-nma.com/	
					Risk I	Ratio								
	Follow up days	Follow up days Intervention 1 28 Remdesivir 100 mg² (2 ams 5 24 Remdesivir 100 mg/day² 28 Remdesivir 100 mg/day² 28 Remdesivir 100 mg²day² 28 Remdesivir 100 mg²day² 28 Remdesivir 100 mg²day² 28 Remdesivir 100 mg² 0.34; l² = 0.0%; r² = 0.00 ("dffferent loading dose) ("dffferent loading dose) Risk of Blas Domains: R Biss due to devision from Intended Interventi Biss due to devision from Intended Interventi Biss due to selection of reported result Diss due to selection of reported result	Follow up days Intervention 1 Intervention 2 28 Remdesivir 100 mg² (2 arms 5 & 10days merged) 24 Remdesivir 100 mg²day Standard care 100 mg²day 28 Remdesivir 100 mg²day Standard care 100 mg²day 28 Remdesivir 100 mg²day Standard care 100 mg²day 28 Remdesivir 100 mg²day Placebo 28 Remdesivir 100 mg² Placebo 29 Reid Biss Demains: 100 mg² Total 100 mg² Total events: 100 mg² Total events: 100 mg² 100 mg² Placebo is developing frequention freemoted result Total	28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 24 Remdesivir 100 mg* (2 arms 5 & 10days merged) 24 Remdesivir 100 mg* (3 arms 5 & 10days merged) 28 Remdesivir 100 mg* (3 arms 5 & 10days merged) 28 Remdesivir 100 mg* (3 arms 5 & 10days merged) 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 29 Remdesivir 100 mg* (2 arms 5 & 10days merged) 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 29 Remdesivir 100 mg* (2 arms 5 & 10days merged) 29 Remdesivir 100 mg* (2 arms 5 & 10days merged) 29 Remdesivir 100 mg* (2 arms 5 & 10days merged) 29 Remdesivir 100 mg* (2 arms 5 & 10days merged) 29 Remdesivir 100 mg* (2 arms 5 & 10days merged) 20 Remdesivir merged (2 arms 5 & 10days merged) 21 Remdesivir merged (2 arms 5 & 10days merged) 22 Remdesivir merged (2 arms 5 & 10day	Control progret (mechanical ventilation +/- addition (mechanical ventilation +/- addition) Follow up days Intervention 1 Intervention 2 rl/N1 r2/N2 28 Remdesivir 100 mg*(2 arms 5 & 10days merged) 6/396 6/200 24 Remdesivir 100 mg*(day* Standard care 6/396 6/200 24 Remdesivir 100 mg*(day* Standard care 60/429 79/428 28 Remdesivir 100 mg* Standard care 60/429 79/428 28 Remdesivir 100 mg* Placebo 89/541 122/521 28 Remdesivir 100 mg* Placebo 24/158 13/79 0.34; t ² = 0.0%; t ² = 0.00 (*different loading dose) Total: 1565 1269 18 Bis due to endomination 0 Bis due to endomination 10 Bis due to endomination 104 events: 189 229 Intervention in	Intervention 1 Intervention 2 r1/N1 r2/N2 28 Remdesivir 100 mg² (2 arms 5 & 10days merged) 6/396 8/200 24 Remdesivir 100 mg² (3 arms 5 & 10days merged) 6/396 8/200 24 Remdesivir 100 mg² (3 arms 5 & 10days merged) 6/396 8/200 28 Remdesivir 100 mg² (3 arms 5 & 10days merged) 6/396 8/200 28 Remdesivir 100 mg² (3 arms 5 & 10days merged) 10/41 7/41 28 Remdesivir 100 mg² (3 arms 5 & 10days merged) 9/428 H 28 Remdesivir 100 mg² (3 arms 5 & 10days merged) 9/41 12/2521 Image: 10/41 28 Remdesivir 100 mg² Placebo 89/541 12/2521 Image: 10/41 28 Remdesivir 100 mg² Placebo 24/158 13/79 Image: 10/42 28 Remdesivir 100 mg² Placebo 24/158 13/79 Image: 10/42 29 Merger 10 arms 1 1565 1269 Image: 10/42 Image: 10/42 29 Merger 10 arms 1 1565 1269 Image: 10/42 Image: 10/42 20 Merger 10 arms 1 1565	Intervention 1 Intervention 2 r1/N1 r2/N2 Pollow up days Intervention 1 Intervention 2 r1/N1 r2/N2 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 6/396 8/200	Pollow up days Intervention 1 Intervention 2 r1/N1 r2/N2 28 Remdesivir 100 mg² (2 arms 5 & 10days merged) 6/396 8/200 4 24 Remdesivir 100 mg/day Standard care 100 mg/day 6/396 8/200 4 28 Remdesivir 100 mg/day Standard care 10/41 60/429 79/428 4 28 Remdesivir 100 mg/day Standard care 10/41 60/429 79/428 4 28 Remdesivir 100 mg²day Placebo 89/541 122/521 4 28 Remdesivir 100 mg² Placebo 89/541 122/521 4 28 Remdesivir 100 mg² Placebo 24/158 13/79 4 4 28 Remdesivir 100 mg² Placebo 24/158 12/521 4 4 4 28 Remdesivir 100 mg² Placebo 24/158 13/79 4 4 4 4 28 Remdesivir 100 mg² Total: 1565 1269 4 4 4 4 4 4 4 4 4 4 4 4	Which progression score level / or above / or	Which progression score level / 2 of above D22 Intervention 1 Intervention 2 r1/N1 r2/N2 Risk Risk Risk 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 6/396 8/200 Image: Colspan="2">Image: Colspan="2" Image: Colspan="2" Image	Which progression score level 7 or above D23 Intervention 1 Intervention 2 r1/N1 r2/N2 A B C D 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 6/396 8/200 Image: C D 24 Remdesivir 100 mg/day* Standard care 100 mg/day* 6/396 8/200 Image: C D 28 Remdesivir 100 mg/day* Standard care 0/41 60/429 79/428 Image: C D 28 Remdesivir 100 mg/day* Standard care 0/429 60/429 79/428 Image: C D 28 Remdesivir 100 mg* Placebo 89/541 122/521 Image: C D 28 Remdesivir 100 mg* Placebo 24/158 13/79 Image: C D 28 Remdesivir 100 mg* Placebo 24/158 12/52 Image: C D D 28 Remdesivir 100 mg* Placebo 24/158 12/9 Image: C D D 8 Back do evident rem intended intervention 189 229 Image: C D D D 8	WHO progression score level 7 of above D22 Intervention 1 Intervention 2 r1/N1 r2/N2 A B C D E 28 Remdesivir 100 mg ⁴ (2 arms 5 & 10days merged) 6/396 8/200 Image: C D E 24 Remdesivir 100 mg ⁴ (2 arms 5 & 10days merged) Standard care 6/396 8/200 Image: C D E 28 Remdesivir 100 mg ⁴ (3y ²) Standard care 6/396 8/200 Image: C D E 28 Remdesivir 100 mg ⁴ (3y ²) Standard care 60/429 79/428 Image: C D E 28 Remdesivir 100 mg ⁴ (2) Placebo 89/541 122/521 Image: C D E <td>Which progression score level is both level is approximate the control above by 23 Intervention 1 Intervention 2 r1/N1 r2/N2 A B Risk of Dias C D E Overall 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 6/396 8/200 Image: colspan="2">Image: colspan="2" colspa="2" colspa="2" colspa="2" colspan="2" colspa="2" colspan="2" col</td>	Which progression score level is both level is approximate the control above by 23 Intervention 1 Intervention 2 r1/N1 r2/N2 A B Risk of Dias C D E Overall 28 Remdesivir 100 mg* (2 arms 5 & 10days merged) 6/396 8/200 Image: colspan="2">Image: colspan="2" colspa="2" colspa="2" colspa="2" colspan="2" colspa="2" colspan="2" col	

Figure 7. Pooled effect of remdesivir on clinical deterioration using the WHO progression score among hospitalized patients (Source: https://www.covid-nma.com)



Study	Study Duration days	Intervention 1	Intervention 2	N1	N2			A	F B	lisk o C	f Bias D	E	Overal	I Estimate [95% CI]
Mild to severe														
Spinner CD, 2020	28	Remdesivir	Standard care	396	200	-								42.99% 1.15 [0.99, 1.34]
Mild to critical		100 mg* (2 arms 5 8	10days merged)											
Ader F, 2021	28	Remdesivir	Standard care	429	428	•								40.38% 0.94 [0.80, 1.11]
Severe		100 mg/day*												
Wang Y, 2020	28	Remdesivir 100 mg*	Placebo	158	79			•	•					16.63% 1.23 [0.87, 1.74]
Heterogeneity: Q = 3.99, p	= 0.14; $l^2 = 50.7\%$; $\tau^2 = 0.0$	1												
Risk of bias ratings: Low Risk of Bias Some Concerns High Risk of Bias	Pisk of E A: Bias due to randor B: Bias due to deviat C: Bias due to deviat D: Bias due to schoo E: Bias due to schoo E: Bias due to schoo	Catterent loading dose) lias Domains: mization on from intended interventio g data ne measurement on of reported result	- Tot	al: 983 Interv	707 vention 2 better 	1.9 lazard Ra	Intervent	tion 1 t	better		Data s	iource:	the COVID-N	1.07 [0.91, 1.27] MA initiative (https://covid-nma.com/)

Time to clinical improvement



		R	emdesivir	Standard of care		Rate Ratio	F	late Ratio		
Study or Subgroup	log[Rate Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Ra	indom, 95% C	1	
1.16.1 Moderate										
Spinner 2020	0.13976	0.07722	396	200	42.2%	1.15 [0.99, 1.34]		-		
Subtotal (95% CI)			396	200	42.2%	1.15 [0.99, 1.34]		٠		
Heterogeneity: Not a	pplicable									
Test for overall effect	Z = 1.81 (P = 0.07	7)								
1.16.2 Severe										
Beigel 2020	0.25464	0.0711	541	521	49.8%	1.29 [1.12, 1.48]		-		
Wang 2020	0.20701	0.17829	158	79	7.9%	1.23 [0.87, 1.74]		+		
Subtotal (95% CI)			699	600	57.8%	1.28 [1.13, 1.46]		•		
Heterogeneity: Tau ²	= 0.00; Chi ² = 0.06	, df = 1 (P = 1	0.80); I ² = 09	6						
Test for overall effect	Z = 3.76 (P = 0.00	002)								
Total (95% CI)			1005	800	100.0%	1 22 [1 11 1 35]				
Total (55% Cl)	0.00.01.7.4.00		1035	000	100.0%	1.22 [1.11, 1.33]	1	•	7	
Heterogeneity: Tau-	= 0.00; Chi* = 1.20	, $at = 2 (P = 1)$	0.55); 1* = 09	6			0.01 0.1	1	10	10
Test for overall effect	z = 4.03 (P < 0.00)	J01)	0.00000	000000			Favours standard of o	are Favours	remdesivir	
Test for subaroup di	fferences: Chi ² = 1	.14. df = 1 (P	$P = 0.29$), $ ^2 =$	12.0%						

Figure 9. Pooled effect of remdesivir on recovery rate among hospitalized patients



				Pato Patio	Pato Patio
Study or Subgroup	log[Rate Ratio]	SE	Weight	IV. Random, 95% CI	IV. Random, 95% CI
1.14.1 Not receiving	oxygen				
Beigel 2020	0.25464	0.17822	13.9%	1.29 [0.91, 1.83]	
Spinner 2020	0.10436	0.107187	28.8%	1.11 [0.90, 1.37]	÷
Subtotal (95% CI)			42.7%	1.16 [0.96, 1.38]	•
Heterogeneity: Tau ² =	: 0.00; Chi ² = 0.52,	df = 1 (P =	0.47); I ² =	0%	
Test for overall effect:	Z = 1.57 (P = 0.12	2)			
1.14.2 Receiving Oxy	gen				
Beigel 2020	0.37156	0.1063	29.1%	1.45 [1.18, 1.79]	-
Subtotal (95% CI)			29.1%	1.45 [1.18, 1.79]	◆
Heterogeneity: Not ap	plicable				
Test for overall effect:	Z = 3.50 (P = 0.00	105)			
1.14.3 Receiving high	n flow oxygen or r	on invasiv	e mechar	nical ventilation	
Beigel 2020	0.08618	0.18508	13.1%	1.09 [0.76, 1.57]	+
Subtotal (95% CI)			13.1%	1.09 [0.76, 1.57]	◆
Heterogeneity: Not ap	plicable				
Test for overall effect:	Z = 0.47 (P = 0.64)			
1.14.4 Receiving me	chanical ventilatio	on or ECMO			
Beigel 2020	-0.0202	0.16943	15.1%	0.98 [0.70, 1.37]	-
Subtotal (95% CI)			15.1%	0.98 [0.70, 1.37]	◆
Heterogeneity: Not ap	plicable				
Test for overall effect:	Z = 0.12 (P = 0.91)			
Total (95% CI)			100.0%	1.20 [1.04, 1.39]	•
Heterogeneity: Tau ² =	0.01; Chi ² = 5.54,	df = 4 (P =	0.24); 2 =	28%	
Test for overall effect:	Z = 2.45 (P = 0.01)			U.U1 U.1 1 1U 1UU Eavours placebo, Eavours remdesivir
Test for subgroup diff	ferences: Chi ² = 5.	02, df = 3 (F	^o = 0.17),	I ² = 40.2%	avours placebo Pavours territesivii

Figure 10. Subgroup analysis according to oxygen requirement on recovery rate among hospitalized patients

	Remde	sivir	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% Cl
Abd-Elsalam 2021	11	100	6	100	7.4%	1.38 [0.58, 3.27]	
Ader 2021	60	339	87	344	22.2%	0.70 [0.52, 0.94]	— •—
Ali 2022	46	634	69	647	20.4%	0.53 [0.38, 0.74]	_ -
Belgel 2020	52	402	82	364	21.3%	0.57 [0.42, 0.79]	_
WHO 2022	535	3787	593	3782	28.7%	0.90 [0.81, 1.00]	-
Total (95% CI)		5262		5237	100.0%	0.72 [0.55, 0.94]	•
Total events	704		859				
Heterogeneity: Tau ² =	0.06; Cl	h ² = 16	l ² = 76% -				
Test for overall effect:	Z = 2.42	? (P = 0	Favours Remdesivir Favours Control				

Figure 11. Pooled effect of remdesivir on need for mechanical ventilation among hospitalized patients



Figure 12. Pooled effect of remdesivir on adverse events among hospitalized patients





Figure 13. Pooled effect of remdesivir on serious adverse events among hospitalized patients

Adverse events



Figure 14. Pooled effect of remdesivir on adverse events among outpatients (Source: https://www.covid-nma.com)



	Serious adverse events													
Study	Study duration	Intervention 1	Intervention 2	r1/N1	r2/N2				Pick	of Bia	e		Weights	Risk ratio 195% CI1
,	days	merrendon i	interrention 2		12/12		А	в	C	D	E	Overall	(%)	
Outpatients Gottlieb RL, 2021	28	Remdesivir 100 mg/day*	Placebo	5/292	19/292	⊢ ∎–1	-			•	-		100.00%	0.26 [0.10, 0.70]
Risk of bias ratings: Low Risk of Bias Some Concerns High Risk of Bias	Risk A: Bias due to ra B: Bias due to ra C: Bias due to m D: Bias due to se E: Bias due to se	(*different loading dose) of Bias Domains: ndomization valion from intended interve ssing data tcome measurement lection of reported result	Total:	292 5	292 19 Intervention C 0.02	1 better	Intervention	2 bett	er	Data	a sour	rce: the COVIC	9-NMA initiativ	0.26 [0.10, 0.70] e (https://covid-nma.com/)

Figure 15. Pooled effect of remdesivir on serious adverse events among outpatients (Source: https://www.covid-nma.com)



Appendix 7: Table of Ongoing Studies

No.	Study Title	Interventions	Status
1	Factorial Randomized Trial of Remdesivir and Baricitinib Plus Dexamethasone for COVID-19 (the AMMURAVID Trial)	Drug: Baricitinib Oral Tablet [Olumiant] Drug: Remdesivir Drug: Dexamethasone	Not yet recruiting
2	IFN-beta 1b and Remdesivir for COVID19	Drug: Interferon beta-1b Drug: Remdesivir	Recruiting
3	Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19)	Drug: Remdesivir	Recruiting
4	Remdesivir in COVID-19 Lahore General Hospital	Drug: Remdesivir	Recruiting
5	Remdesivir, Long-covid and Quality of Life	Drug: Remdesivir	Recruiting
6	Baricitinib in Hospitalized Covid-19 Patients With Diabetes Mellitus	Drug: Baricitinib Drug: Dexamethasone Drug: Remdesivir	Recruiting
7	Efficacy of Remdesivir and Baricitinib for the Treatment of Severe COVID 19 Patients	Drug: Remdesivir Drug: Baricitinib Drug: Tocilizumab	Recruiting
8	Efficacy of Favipiravir in Treatment of Mild & Moderate COVID-19 Infection in Nepal	Drug: Favipiravir Drug: Placebo Drug: Remdesivir	Recruiting
9	ACTIV-5 / Big Effect Trial (BET-C) for the Treatment of COVID-19	Drug: Danicopan Other: Placebo Drug: Remdesivir	Recruiting
10	Comparative Therapeutic Efficacy and Safety of Different Antiviral and Anti Inflammatory Drugs in COVID-19 Patients.	Drug: Remdesivir Drug: Hydroxychloroquine Drug: Tocilizumab Drug: Lopinavir/ Ritonavir Drug: Ivermectin	Recruiting
11	Safety, Tolerability and Pharmacokinetics of Inhaled Nanoparticle Formulation of Remdesivir (GS-5734) and NA-831	Drug: NA-831 Drug: Placebo Drug: GS-5734 Combination Product:	Recruiting
		Drugs: NA-831 plus GS-5734	
12	Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients	Drug: Baricitinib Drug: Remdesivir + baricitinib Drug: Remdesivir Drug: Tocilizumab	Recruiting
13	Trial of Treatments for COVID-19 in Hospitalized Adults	Drug: Remdesivir Drug: Lopinavir/ritonavir Drug: Interferon Beta-1A Drug: Hydroxychloroquine	Recruiting



			1
		Other: Standard of care Drug: AZD7442 Other: Placebo	
14	ACTIV-3b: Therapeutics for Severely III Inpatients With COVID-19	Biological: Remdesivir Drug: Remdesivir Placebo Biological: Aviptadil Drug: Aviptadil Placebo Drug: Corticosteroid	Recruiting
15	Austrian CoronaVirus Adaptive Clinical Trial (COVID-19)	Drug: Chloroquine or Hydroxychloroquine Drug: Lopinavir/Ritonavir Other: Best standard of care Drug: Rivaroxaban Drug: Thromboprophylaxis Drug: Candesartan Drug: non-RAS blocking antihypertensives Drug: Remdesivir Drug: Asunercept 400mg Drug: Asunercept 100mg Drug: Asunercept 25mg Drug: Pentaglobin	Recruiting
16	Trial to Determine the Efficacy/Safety of Plitidepsin vs Control in Patients With Moderate COVID-19 Infection	Drug: Plitidepsin Drug: Dexamethasone Drug: Remdesivir	Recruiting
17	I-SPY COVID-19 TRIAL: An Adaptive Platform Trial for Critically III Patients	Drug: Remdesivir Drug: Pulmozyme Drug: IC14 Drug: Celecoxib Famotidine Drug: Narsoplimab Drug: Aviptadil Acetate Drug: Cyclosporine	Recruiting
18	Finding Treatments for COVID-19: A Trial of Antiviral Pharmacodynamics in Early Symptomatic COVID-19 (PLATCOV)	Drug: Favipiravir Drug: Monoclonal antibodies Drug: Ivermectin Other: No treatment Drug: Remdesivir	Recruiting
19	Assessment of utility of Remdesivir in Patients with Acute Kidney Injury or Chronic Kidney Disease in admitted COVID-19 patients	Drug: Remdesivir	Recruiting
20	REMdesivir-HU Clinical Study and Severe Covid-19 Patients	Drug: Remdesivir-HU	Not recruiting
21	Study to Evaluate the Efficacy and Safety of Remdesivir in Participants With Severely Reduced Kidney Function Who Are Hospitalized for Coronavirus Disease 2019 (COVID-19)	Drug: Remdesivir	Not recruiting
22	ACTIV-5 / Big Effect Trial (BET-B) for the Treatment of COVID-19	Biological: Lenzilumab Drug: Remdesivir	Not recruiting
23	SARS-CoV-2 Human Challenge Characterisation Study	Drug: Remdesivir	Not recruiting



24	ACTIV-3: Therapeutics for Inpatients With COVID-19	Biological: LY3819253 Drug: Placebo Biological: Remdesivir Biological: VIR-7831 Biological: BRII-196/BRII-198 Biological: AZD7442 Drug: MP0420	Not recruiting
25	Antiviral Activity and Safety of Remdesivir in Bangladeshi Patients With Severe Coronavirus Disease (COVID-19)	Drug: Remdesivir	Completed
26	Efficacy and Safety of Remdesivir and Tociluzumab for the Management of Severe COVID-19: A Randomized Controlled Trial	Drug: Remdesivir Drug: Tocilizumab	Completed
27	Study in Participants With Early Stage Coronavirus Disease 2019 (COVID-19) to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation	Drug: Remdesivir	Completed
28	Remdesivir Efficacy In Management Of COVID-19 Patients	Drug: Remdesivir	Completed
29	Effectiveness of Remedesvir in COVID-19 Patients Presenting at Mayo Hospital Lahore	Drug: Remdesivir	Completed
30	ACTIV-5 / Big Effect Trial (BET-A) for the Treatment of COVID-19	Other: Placebo Drug: Remdesivir Biological: Risankizumab	Completed
31	Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	Drug: Baricitinib Drug: Dexamethasone Other: Placebo Drug: Remdesivir	Completed
32	The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients	Drug: Hydroxychloroquine Drug: Remdesivir Other: (Standard of Care) SoC	Unknown
33	Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN)	Drug: Remdesivir	Recruiting